CLINICAL AND EXPERIMENTAL ASPECTS OF XANTHOMATOSIS*

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INTRODUCTION

Though in 1873 Fagge mentioned for the first time the complications in the heart and aorta in xanthomatosis and Török (19) and Arning (2) described cases of sudden death in this condition, only during recent decades has the relation between xanthomatosis of the skin and of the circulatory system been stressed. Of the 11 xanthelasma tuberosum multiplex (x.t.m.) patients we examined since 1930, 6 died suddenly, 3 of them under 20 years, one is living but is suffering from angina pectoris and one was an invalid from claudicatio intermittens for a long time before his cardiac death. Data on the blood chemistry of these patients are given in table I. It is evident that the lipid values are markedly enhanced, the relation between the lipid fraction is in some cases normal, in other abnormal, the blood sugar is always normal.

In 1938 Montgomery and Osterberg (8) found in 28% of their cases of x.t.m. severe cardiovascular damage. About the same time Carl Müller (9) and Thanhauser-Magendantz (18) stressed the fact that xanthoma patients often suffer from angina pectoris or die suddenly.

The great frequency of systemic complications in x.t.m. became particularly interesting because of the insight into the pathogenesis of coronary thrombosis and arteriosclerosis that might be gained from this fact.

It is well known that it is possible to induce in rabbits xanthoma of the skin and atheromatosis of the aorta by feeding cholesterol to them (18, 15, 17, 5). We undertook similar experiments in order to investigate more closely the blood chemistry under these circumstances. Then we wished to ascertain whether there is a correlation between the various symptoms caused by cholesterol feeding and the different changes observed in the blood.

We were interested in the pathological changes to be found in the eyes because an arcus lipoides corneae is often observed in patients with coronary diseases. Various authors deemed this arcus an important symptom and have speculated on the pathological meaning of this disturbance.

Finally it was our aim to ascertain if iodine compounds act favorably on this experimental cholesterosis of the rabbit. The reports in the literature on this subject had thus far been rather conflicting, but a favorable influence of iodine on hypertension has been taken for granted. In the cardiologic journals papers on this subject appear regularly. Page (11) claimed in 1952 again that iodine can protect animals against cholesterol deposition.

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TABLE I

Blood chemistry in 11 xanthoma patients

	SEX	AGE	TOTAL CHOL. MG. PER 100 CC.	FREE CHOL. MG. PER 100 CC.	PERCENTAGE CHOL. ESTERS	P. LIPIDS MG. P. PER 100 CC.	QUOTIENT TOT. CHOL./P. LIPIDS	QUOTIENT CHOL. ESTERS /P. LIPIDS	TOTAL FATTY ACIDS	BLOOD SUGAR MG. PER 100 CC.	CARDIOVASCULAR COMPLICATIONS
1 H.v.T.	m	18	740	201	72	24.2	35.8	22.3	1630		angina pectoris
2 H.v.T.Sr.	m	34	334	108	68	13.6	24.5	16.6	730		Father of 1. At the time of examination extensive xanthelasmata palpebralia; at 40 y. angina pectoris, at 44 y. sudden death, presumably coronary thrombosis
3 P.R.	f	11	1080			22.8	47.3		1140	118	cardiac death
4 P.P.R.	m	14	399	151	62	22.6	17.7	11.0	633	109	sudden death
5 M.R.	m	7	836			17.3	48.3		940	102	sudden death
6 Sch.	m	50	596			17.8	33.5		1830	90	normal at the time of examination; no follow up
7 S.	f	40	499			15.8	31.6		1020	95	as 6
8 D.P.	m	45	323	105	68	13.0	24.7	16.7	1134		as 6
9 A.v.T.	m	61	400			16.4	24.4		568		died from coronary thrombosis
10 K.K.	f	55	407	188	56	19.0	21.4	12.1	795	94	died from coronary thrombosis
11 J.R.	m	43	576	160	72	20.1	28	20			claudicatio intermittens; cardiac death

Normal values:	* Total cholesterol:	213 ± 44	± 10 mg. per 100 cc.
	* Free cholesterol:	72 ± 22	± 5 mg. per 100 cc.
	* Percent. Chol. esters:	67 ± 7	± 2
	* P. lipids:	8.9 ± 1.2	± 0.3 mg. P per 100 cc.
	* Quot. Chol./P. lipid:	24.0 ± 4.6	± 1
	* Quot. Chol. esters/P. lipid:	16.0 ± 3.5	± 0.8
	† Total fatty acids:	190 – 420 mg. per 100 cc.	

* Polano, M. K., 1941.

† Thanhauser, 1950.

METHODS

We started our experiments with 18 male juvenile chinchilla rabbits to which we administered 4 times a week 1 Gm. cholesterol and 5 cc. peanut oil. The maximum cholesterol value after 175 days was 869 mg. per cent, the minimum 212 mg.: respectively more than nine times and more than twice the initial value.

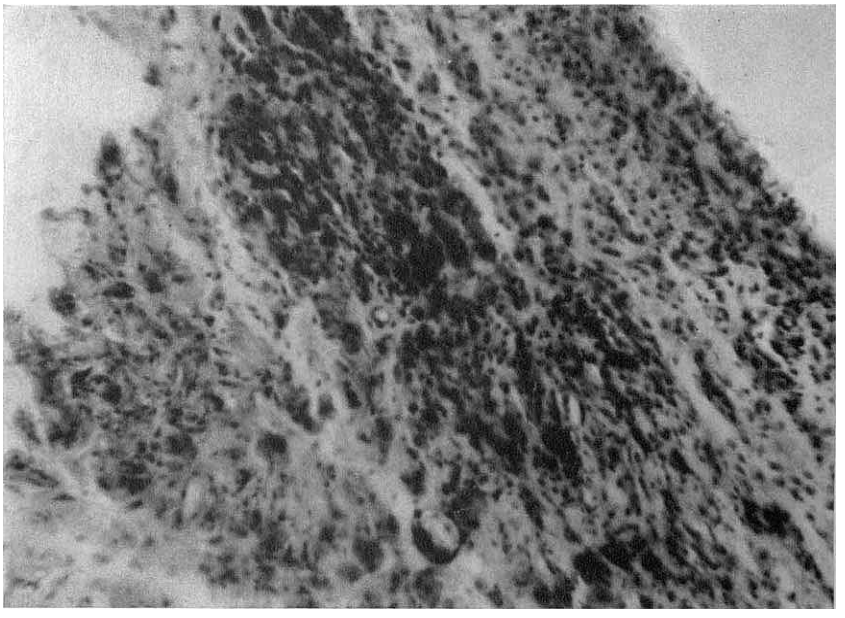

FIG. 1. Lipid deposits in the skin around a celloidin cube

We then divided the animals into three groups in such a way that the average cholesterol content of each group was approximately the same. Then in one group we added 0.4 Gm. potassium iodide daily to the cholesterol feeding, in the second group an equivalent iodide dosage in the form of an organic iodine compound: ricinic stearyl alcohol diiodide (dijodyl) was given, and in the third (control) group cholesterol alone was continued. The methods we employed are more fully discussed in an earlier paper (14).

To provoke xanthoma formation we irritated the skin of the rabbits artificially in three different ways. We introduced small cubes of celloïdine under the skin; we pinched the skin with metal agraves, and finally we put a thread through the skin. On the 257th day the animals were killed and the various organs examined microscopically.

EXPERIMENTAL DATA

The methods we used to irritate the skin had caused the appearance of xanthomatous formations in most animals (fig. 1). In a few cases, spontaneous xanthoma formation arose as well. The eyes of the rabbits were examined by Dr. Pieck, who found in some cases lipid deposits in the cornea. Still more marked alterations were seen in sclera, corpus ciliare and iris, which however differ essentially from the human arcus senilis. [The liver and adrenal glands showed a more or less pronounced lipid infiltration in all cases.]

Finally the hearts of the animals were cut in series and the aorta with the great vessels were examined macro- and microscopically. Marked atheromatosis of the aorta and coronary arteries, to a lesser extent also of the pulmonary artery, was observed (figs. 2, 3 and 4).

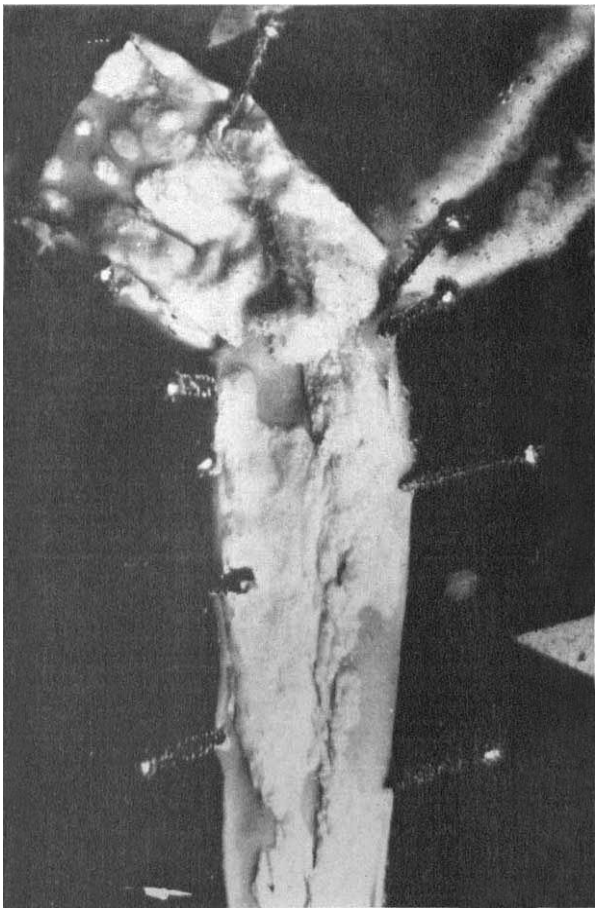

FIG. 2. Atheromatous changes of the aorta

The pathological changes in the various organs were evaluated by indices. The skin xanthomatosis index was found by correlating the xanthoma formation with the various forms of irritation. The spontaneous xanthoma formation was graded 1–4+ and the total was divided by the number of sites examined. The eye xanthomatosis index was calculated in a similar way. The fatty infiltration of the liver was evaluated from 1 to 4.

In several rabbits there was a very marked atheromatosis of the aorta (C1, B2, B3) in others these changes were slight or nonexistent (B5, B6, C6). In order to give some idea of the changes observed the macroscopic and microscopic atheromatosis changes were evaluated from 1 to 6 for the aorta ascendens, the aorta descendens immediately below the arcus, the aorta descendens just over the diaphragma and the abdominal aorta. It was striking that contrary to what is usual seen in humans, atheromatosis of the aorta abdominalis was always the least pronounced, while the aorta ascendens, was among the most affected parts.

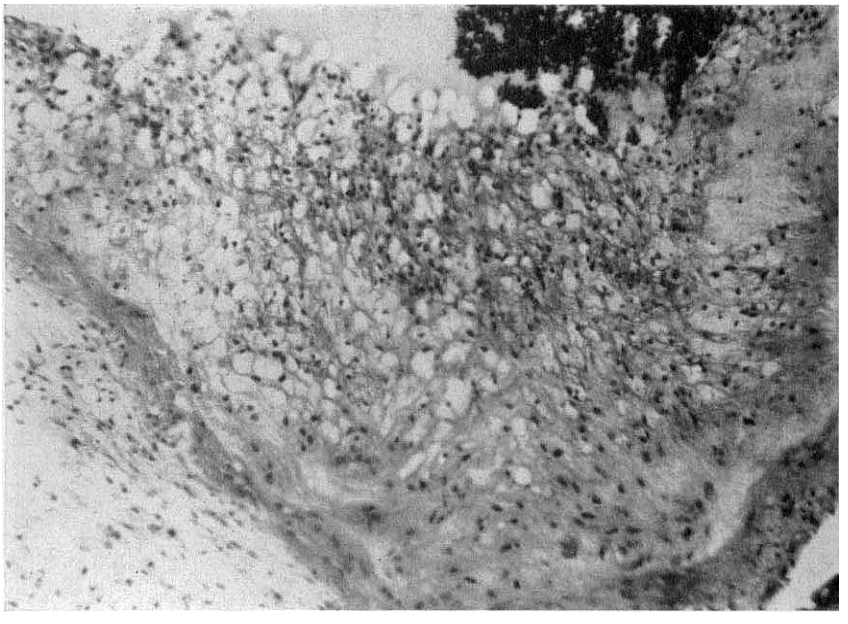

FIG. 3. Internal thickening of coronary artery (foam cells)

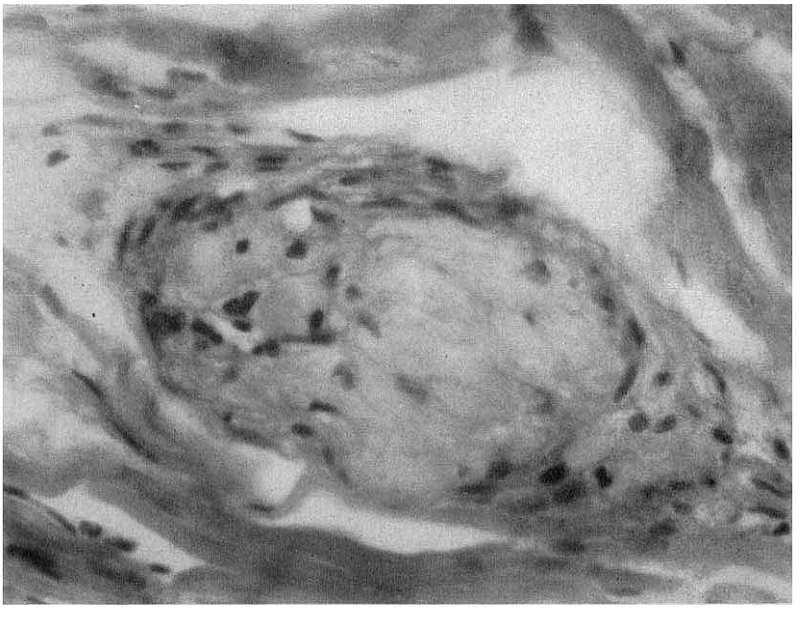

FIG. 4. Obliteration of small coronary branch in the myocardium

TABLE II

	TOTAL CHOL. MG. PER 100 CC.	FREE CHOL. MG. PER 100 CC.	PER CENT CHOL. ESTERS	P. LIPIDS MG. PER CENT P.	QUOTIENT TOT. CHOL./P. LIPID	QUOTIENT CHOL. EST./P. LIPID
Average at the beginning of the experiments	90	68	26	10.0	9.3	2.3
Average Group I (Cholesterol-feeding for 259 days)	885	223	74	20.2	34.7	32.9
Average Group II (Cholesterol-feeding for 259 days, during the last 72 days in addition dijodyl)	2000	616	70	37.4	51.0	37.5
Average Group III (Cholesterol-feeding for 259 days, during the last 72 days in addition KJ)	1540	437	71	33.2	45.7	33.6

TABLE III

SEQUENCE ACCORDING TO THE BLOOD CHOLESTEROL CONTENT AT THE END OF THE EXPERIMENT		CHOL. CONTENT AFTER 175 DAYS	CHOL. CONTENT AFTER 259 DAYS	QUOT. CHOLESTEROL ESTERS/P. LIPIDS	SKIN XANTHOMATOSIS INDEX		EYE XANTHOMATOSIS INDEX		LIVER XANTHOMATOSIS INDEX		AORTA ATHEROMATOSIS INDEX	
Group I Chol. content more than 3000 mg/100 cc.	1 C1D	550	3287	50.0	1.5		2.4		4		5	
Group II Chol. content 2000–3000 mg/100 cc.	2 B4D	869	2635	32.6	1.75	1.5	1.2	1.1	4	3.5	3.25	3.5
	3 B2KI	414	2231	34.0	1		1.4		2		5	
	4 B3KI	837	2070	37.3	1.75		1.6		4		5	
	5 C6D	385	2005	37.0	1		0.1		4		0.5	
Group III Chol. content 1000–2000 mg/100 cc.	6 B5KI	378	1722	39.1	1.25	1.25	0.1	0.5	2.5	2	0.5	1.75
	7 A2D	347	1487	38.2	1.25		0.8		1		2.25	
	8 C2D	221	1315	32.8	0.5		0.1		2		1	
	9 A6C	540	1257	40.3	1		0.4		2		1	
	10 A5D	244	1225	34.6	1		0.1		2.5		0.75	
	11 C5C	514	1219	39.9	2		0.6		2.5		2	
	12 A1D	471	1208	37.4	1		1.3		2		2.25	
	13 B1KI	240	1036	26.0	2.25		0.7		2		4	
Group IV Chol. content less than 1000 mg/100 cc.	14 B6KI	370	885	28.0	1.25	1.25	0	0.2	2	1.75	0.25	1.25
	15 C3C	212	682	25.0	1		0.1		1		1	
	16 A3C	550	670	27.6	1.75		0.5		3		2.5	
	17 C4C *	234	596	26.9	1		0.2		1		1.5	

The first letter and number relate to the cages of the animals, the last letter means D for Dijodyl, KI for potassium iodide and C for controls, which received only cholesterol/oil mixture.

* In this table only 17 animals are listed, the 18th died spontaneously during the experiments.

The result of the experimental period on the blood chemistry and the xanthoma formation is given in the tables II and III.

COMMENT

It becomes obvious that the cholesterol and oil caused a marked rise in the lipid content of the blood of the rabbits. Next to this both iodine preparations had also a distinct effect: they gave an additional rise, the effect of the organic iodide compound being the stronger one.

From the figures it becomes evident that the increase in the cholesterol content is the most pronounced, and that this rise can, in the first place, be attributed

to the cholesterol esters. [In normal rabbits only 26% of the total cholesterol in the blood is esterified, after cholesterol feeding without addition of iodine this percentage was more than 70%.] It must be stated at the same time that the iodine compound pushed up the cholesterol level in a special way: the *additional* rise of the cholesterol by the dijodyl and KI is for a considerable part caused by free cholesterol.

Similarly in the humans with xanthoma, the phospholipid content in the blood of the rabbits is plainly increased—two-fold in the control series, almost four times in the dijodyl series. This increase is much less than that of the cholesterol values, resulting in a rise of the ratio total cholesterol/phospholipid and cholesterol ester/phospholipid.

We computed the correlation coefficient between final values for the total cholesterol content of the blood and the quotient cholesterol esters/phospholipids, the last mentioned being deemed the most important index of the so-called dyslipoïdaemia. This correlation was found to be 0.71 with a p between 0.01 and 0.001, which indicates that the correlation is significant. In view of this fairly high grade of correlation in respect to the size of the material, the question whether the dyslipoïdemia is more important than the cholesterol content for the arising of xanthomatosis, as was claimed by Bloch (3) and Schaaf (16) and of coronary xanthomatosis as recently was claimed by Gertless (7) and coworkers loses much of its importance.

This coincides with the fact that we encountered neither in patients with xanthomatosis with heart diseases, nor in the rabbits, cases in which one of the quotients was pathologic while the absolute value was normal. So nothing proves the preponderant importance of the quotients.

When we inquire into the nature of the additional rise in lipid content of the blood caused by iodine administration we see that several possibilities exist. The absorption from the intestine might be enhanced, or the excretion diminished. In both cases an increase of the lipid depots is to be expected. On the other hand it could be possible that this rise of the lipid components of the blood were due to a liquidation of depots.

The microscopic examination of the rabbits* proved one of the first two assumptions to be true. In all rabbits some relation between the degree of lipemia and the degree of lipid deposition could be observed.

The animals were once listed according to the cholesterol content of the blood after 175 days of cholesterol/oil feeding alone; once according to the same content after the additional 72 days.

As was expected the best correlation between the blood-values and the organ pathology could be established when the rabbits were listed according to the cholesterol content of the blood at the end of the experiment. This sequence is therefore given in table III.

Next to this it is remarkable that two rabbits living under exactly the same circumstances (f.i. C1D and A5D; A6C and C4C) may react quite differently to

*The authors gladly acknowledge the friendly and excellent help they received form Dr. H. J. G. Wijers, Pathologist of the Hospital of Joannes de Deo, The Hague.

the enhanced cholesterol level in the blood. The susceptibility for cholesterol of the various organs must be different from one animal to the other.

CONCLUSIONS

The lipid content of the blood is important in the pathogenesis of atheromatosis and xanthomatosis in rabbits. There exists a direct correlation (R: 0.71 $p \ll 0.01 > 0.001$) between the cholesterol content of the blood and the quotient cholesterol esters/phospholipids. In rabbits, in which the blood cholesterol is pushed up by iodine (organic and inorganic), the atheromatosis and xanthomatosis runs nevertheless parallel with the cholesterol content of the blood. This proves that iodine has no therapeutic value in these cases.

A parallel is drawn between these experiments and human pathology. Though the lipid level in the blood plays a part in the pathogenesis of aorta- and coronary-atheromatosis and skin xanthomatosis, the marked differences between the rabbits living under almost identical circumstances, point to constitutional variations of susceptibility as another important factor. The possible influence of a local factor is evident from both the well-known pathology of human xanthomatosis and from the effect of local irritation on the skin of the hypercholesterolemic rabbit.

SUMMARY

Considering the relation between xanthelasma tuberosum multiplex and vascular and cardiac atheromatosis, experiments in rabbits were performed to ascertain how far changes in the lipid content of the blood could be considered as a common cause of x.t.m. and atheromatosis of aorta and coronary vessels. The action of iodine compounds on these conditions and on the lipid content of the blood was estimated. By feeding a cholesterol/oil mixture to rabbits, not only a considerable increase of the cholesterol content of the blood, but also a rise in the phospholipid content and the quotients indicating the relation between cholesterol and its esters to the phospholipids could be caused. A direct correlation between the total cholesterol content and the quotient cholesterol esters/phospholipids could be established. Iodine administration increased the effect of cholesterol feeding. The individual reaction of the animals differed considerably. The pathological findings included xanthoma formation in the skin, chiefly on artificially irritated places, atheromatosis of the aorta and coronary vessels, liver, adrenal glands and eyes. The relation between the severity of the involvement of the various organs showed a relation to the degree of hypercholesterolemia, but could not be explained by the blood changes alone. Local and individual causative factors act in addition to the changes in the blood induced by cholesterol feeding.

REFERENCES

1. Anitschkow, N.: Zur Aetiologie der Atherosklerose. Virchow's Arch. f. path. Anat., 249: 73–82, 1924.
2. Arning, E.: Ein Fall von familiärer Xanthomatose. Arch. f. Dermat. u. Syph., 105: 290–291, 1910.

3. Bloch, B.: Metabolism, endocrine glands and skin-diseases, with special reference to acne vulgaris and xanthoma. Brit. J. Dermat., 43: 61–87, 1931.
4. Duff, G. L., and McMillan, G. C.: Pathology of atherosclosis. Am. J. Med., 11: 92–108, 1951.
5. Duff, G. L.: Nature of experimental cholesterol arteriosclerosis in rabbit. Arch. Path., 22: 161–182, 1936.
6. Fagge, E. H.: General xanthelasma or vitiligoidea. Tr. Path. Soc. London. 1873.
7. Gertless, M. M.: The interrelationships of serum cholesterol, cholesterol esters and phospholipids in health and in coronary artery disease. Circulation, 2: 205–214, 1950.
8. Montgomery, H., and Osterberg, A. E.: Xanthomatosis; correlation of clinical, histopathologic and chemical studies of cutaneous xanthoma. Arch. Dermat. Syph., 37: 373–402, 1938.
9. Müller, C.: Xanthoma, hypercholesterolemia, angina pectoris. Acta med. Scandinav., Suppl. 89: 75–84, 1938.
10. Page, I. H., and Brown, H. B.: Induced hypercholesterolemia and atherogenesis. Circulation, 6: 681–687, 1952.
11. Page, I. H., and Bernhard, W. G.: Cholesterol induced atherosclerosis. Its prevention in rabbits by the feeding of an organic iodine compound. Arch. Path., 19: 530–536, 1935.
12. Pick, L., and Pinkus, F.: Weitere Mitterlung zur Lehre von den Xanthomen. Dermat. Wchnschr., 49: 160–162, 1909.
13. Polano, M. K.: Die Xanthelasmatosen der Haut. Arch. f. Dermat. u. Syph., 181: 139–172, 1940.
14. Polano, M. K.: Experimental hyperlipoidaemia in the rabbit and influence of iodine-preparations on this hyperlipoidaemia. Arch. internat. de pharmacodyn. et de thérap., 86: 1–16, 1942.
15. Rohrschneider, W.: Beitrag zur Kenntnis der experimentellen Hypercholesterinämie des Kaninchen. Virchow's Arch. f. path. Anat., 256: 139–149, 1925.
16. Schaaf, F.: Experimentelle Beiträge zur Pathogenese der Xanthome. (xanthomentstehung und lipidstoffwechsel beim kaninchen nach lanolinfütterung). Arch. f. Dermat. u. Syph., 175: 279–333, 1937.
17. Schönheimer, R.: Experimentelle Venen-Atherosklerose. Virchow's Arch. f. path. Anat., 251: 732–738, 1924.
18. Thanhauser, S. J. and Magendantz, H.: The different clinical groups of xanthomatous diseases; A clinical physiological study of 22 cases. Ann. Int. Med., 11: 1662–1746, 1938.
19. Török, L.: De la Nature des Xanthomes avec Quelques Remarques Critiques sur la Notion des Tumeurs. Ann. de dermat. et Syph., 4: 1109–1273, 1911.
20. Thanhauser, S. J.: Lipidoses, Diseases of the cellular lipid metabolism, Oxford University Press, N. Y. 1950.